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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/618,235	07/18/2000	Donn Nelson Rubingh	7670	8554

27752 7590 09/09/2002

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EXAMINER

MOORE, WILLIAM W

ART UNIT PAPER NUMBER

1652

DATE MAILED: 09/09/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Applicant(s)

09/618,235

Applicant(s)

RUBINGH ET AL.

Examiner

William W. Moore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 21 June 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-21 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-21 are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

## DETAILED ACTION

### *Response to Amendment*

Applicant's Amendment A, Paper No. 14 filed June 21, 2002, has been entered and the amendments to claims 1, 5-7, 11, 12, and 19 avoid the rejections of record of claims 1-21 under the second paragraph of 35 U.S.C. § 112. The pending claims still recite amino acid positions withdrawn from consideration pursuant to Applicant's election of species in Paper No. 9 filed November 2, 2001, and the restriction was made final in Paper No. 11 mailed January 18, 2002. The claims are examined to the extent that they describe proteases modified by substitution and conjugation at positions corresponding to any one positions 17, 52, 89, 134, 155 and 265 of the mature subtilisin BPN'.

### *Information Disclosure Statement*

Applicant's Supplemental Disclosure Statement, Paper No. 15 filed June 21, 2002, is hereby acknowledged. Applicant's provision therewith of copies of three references cited - but not previously considered because the publication dates for all three were unstated - in the Information Disclosure Statement filed December 4, 2000, Paper No. 2, is accepted, and these three references supplied with Paper No. 15 are made of record herewith on the accompanying form PTO-892.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. § 112:  
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-18 are indefinite because claim 5 depends ultimately from claim 1, yet claim 1 is now limited by the amendments of Paper No. 14 to subtilisin BPN' protease conjugates having one or more addition moieties covalently attached to an amino acid at a recited position, while claim 5 describes several other proteases as well as subtilisin BPN'.

Thus there is no antecedent basis in claim 1 for the recitation of claim 5. Claims 6-18 are included in this rejection because they depend from claim 5, thus incorporate its indefinite description, without resolving the ambiguity of the description of claim 5. Limiting claim 5 to the recitation only of subtilisin BPN' would not overcome this rejection because claim 5 would become redundant with claim 1. Rewriting claim 1, however, as had originally been suggested at page 4, lines 23-25 of Paper No. 11 will overcome this rejection. In the alternative, this rejection may be overcome by canceling claim 5 and by then amending claim 6 to recite a dependency from claim 1.

*Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claims 1-6, 8, 9 and 20 remain rejected for reasons of record under 35 U.S.C. §103(a) as being unpatentable over von der Osten et al., U.S. Patent No. 6,300,116, and Braxton et al., U.S. Patent No. 5,766,897, of record.

Applicant's arguments filed June 21, 2002, have been fully considered but they are not persuasive. Applicant suggests that one of ordinary skill in the art at the time the invention was made would have failed to experience sufficient motivation to combine the teachings of von der Osten et al. and Braxton et al. The rejected claims describe products wherein an epitope region, which is necessarily a region on the surface of the molecule, of at least subtilisin BPN', is masked, or protected from immune surveillance, by conjugation

of an addition moiety to an amino acid in the region, which in claim 4 may be a cysteine substituted for a native amino acid in order to facilitate such protective conjugation. The argument at pages 5-6 of Paper No. 14 is misplaced in asserting that "epitope protection" is a controlling element of the claims because it is Applicant's election of a position in the subtilisin BPN' amino acid sequence that controls the application of prior art publications and because there is no need that the prior art supply the same motivation that Applicant had for making the product so long as the prior art would have motivated one of ordinary skill in the art at the time the invention was made with adequate motivation to make the same product. Applicant indicated, in responding to a restriction requirement for election of a single position/species, positions equivalent in any subtilisin equivalent to six positions in the amino acid sequence of the mature subtilisin BPN', and all six were examined as they were considered to be reasonable number of species for examination. While the prior art discloses amino acid substitutions at five of these six positions, only substitutions at the subtilisin BPN'-equivalent position 134 are disclosed to confer a protective advantage on a resulting product. Indeed, the prior art teaches away from making a protective alteration at the subtilisin BPN'-equivalent position 155. But an altered product that will mask the subtilisin BPN'-equivalent position 134, and the surrounding region, prepared according to teachings of the prior art will inherently have the property that Applicant desired, as well as a property the prior art recognizes to be advantageous.

Von der Osten et al. teach that making a generic amino acid substitution at a position corresponding to the subtilisin BPN' position 134, see Table III at col. 15, will block or inhibit autoproteolysis. The position is susceptible to proteolysis because it is exposed in a region on the surface of any subtilisin, see Table III, and artisans at the time the invention was made, reading the teaching of von der Osten et al., would have readily recognized that protecting position 134 in the subtilisin BPN' amino acid sequence would make a product

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less susceptible to autoproteolysis as well a protecting position 132 in subtilisin 309 less susceptible to autoproteolysis. Such an artisan would also have been aware that masking an exposed position from immune surveillance would also mask it from recognition by the catalytic region of the same, or another, subtilisin, thus preventing autoproteolysis, and

5 Braxton et al. teach that substituting cysteines for native amino acids in a protein and then conjugating polymers to the cysteines, including polyethylene glycol [PEG] polymers, will mask an exposed epitope on an enzyme from immune surveillance. Von der Osten et al. further disclose preparation of detergent cleaning compositions comprising such autoproteolysis-resistant subtilisin variants and the adduct-protected enzymes of Braxton et al. are also taught to be compatible with compositions wherein they are ordinarily used.

10 Thus it would have been obvious for one of ordinary skill in the art to protect proteolysis-susceptible regions of a subtilisin, such as the position corresponding to the subtilisin BPN' position 134 identified by von der Osten et al., by substituting a cysteine for the native amino acid at the subtilisin BPN'-correspondent position 134 and conjugating a PEG

15 polymer to the cysteine with the procedures taught by Braxton et al., resulting in a product that also meets the limitations of claims 1-6, 8 and 9. It would further have been obvious to such an artisan to incorporate a subtilisin having a conjugation of a PEG polymer at the subtilisin BPN'-correspondent position 134 in a cleaning composition of claim 20 because the artisan could reasonably expect that a protease conjugate would be more stable than a

20 corresponding unconjugated subtilisin in its resistance to autoproteolysis. The rejection of record is sustained.

Claim 21 remains rejected for reasons of record under 35 U.S.C. §103(a) as being unpatentable over von der Osten et al. ('116) and Braxton et al., as applied to claims 1-6, 8, 9 and 20 above, and further in view of Powell et al., U.S. Patent No. 6,060,546, made of record herewith.

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Applicant's arguments filed June 21, 2002, have been fully considered but they are not persuasive. Applicant believes that no advantage one of ordinary skill in the art at the

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time the invention was made would recognize in preparing a subtilisin having a substitution of cysteine at the subtilisin BPN' position 134, wherein a masking adduct is conjugated to the cysteine, for use in detergent compositions would also have been recognized by such an artisan to be advantageous in formulation of a personal care composition where both

5 van der Osten et al. and Braxton et al. contemplate use of their modified enzymes in detergent compositions. Powell et al., available as prior art under 35 U.S.C. 102(e) in view of their earlier filing date, teach, see paragraph spanning cols. 16 and 17, the preparation of a personal care composition comprising a subtilisin, thus it would have been

10 obvious to one of ordinary skill in the art at the time the invention was made to prepare a personal care composition according to Powell et al. and substitute a protease conjugate obvious over the teachings of von der Osten et al. and Braxton et al., for that used by Powell et al. because such an artisan at that time would have had a reasonable expectation that a protease conjugate resistant to autoproteolysis would have at least comparable, if not greater, stability and would advantageously fulfill the same role as well as the subtilisin

15 taught by Powell et al. The rejection of record is sustained.

#### Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

20 A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any


25 extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

30 Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 7:00AM-5:30PM EST on Mondays and Wednesdays, between 7:00AM-1:30PM EST on Tuesdays and Thursdays, and between 8:30AM and 5:00PM EST on Fridays. The examiner's direct FAX telephone number is 703.746.3169. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be

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5 reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore  
September 6, 2002

  
PONNATHUR JACHIN MURTHY  
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